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THE ORGANIZATION OF THE INSECT SEGMENT

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INTRODUCTION

During development of multicellular organisms it is essential that individual cells should develop appropriate to their position in the whole. This could be achieved in two basic ways: either the process could be so rigidly programmed that communication between cells becomes unnecessary (mosaic development) or the cells could monitor their position in the whole and make continuous or periodic adjustments (regulative development). In most organisms both mechanisms are employed, the developmental fate of cells being initially plastic so that transposition or loss of parts can be compensated for, but later becoming determined.

This paper makes an attempt to analyse the way cells determine their position in a model system – the insect segment – and the use they make of the information. The insect cuticle is secreted by a single layer of cells, and may contain oriented anisotropic structures, such as bristles, which indicate the polarity of the individual cells which secrete them. This expression of polarity by single cells is an unusual and extremely useful feature of insects, which has revealed the central relationship between polarity and position.

DISCOVERY OF THE INSECT SEGMENTAL GRADIENT

The story begins with some experiments undertaken by Piepho in 1955. Piepho wanted to know how the scales of insects became oriented in a particular way, and realized that operations done on insects prior to the development of scales might indicate the control of this polarity. In the mature caterpillar he rotated a piece of integument through 180 degrees and observed the orientation of scales in the adult. He found that scales in the centre of the rotated piece had been inverted by the operation, but at the edge the orientation of scales was not autonomous to the rotated piece or to the host and that interactions occurred. Here the polarity of the scale-forming cell was influenced both by the orientation of the host and the graft cells. Piepho described these influences as orientating forces, the scale taking up the orientation of the resultant between the two (Piepho, 1955*a*). Piepho (1955*b*) also experimented with the margins of the segment: In the waxmoth *Galleria* each segment has an anterior and posterior margin, and the scales point posteriorally. Transplantation of pieces of these margins into the segment surface altered the polarity of the scales for some distance around. If the anterior margin was used the scales pointed away from the graft, and if the posterior, the scales pointed towards the graft. Although no formal explanation for these results was offered, Piepho concluded that these orienting forces certainly came from the segment margins and also probably from the general area of segment itself.

Locke (1959, 1960) worked with the bug *Rhodnius* which has a different polarity indicator. Instead of densely packed scales, the surface of the abdominal tergites of adult *Rhodnius* is buckled into oriented folds or 'ripples'. These ripples run at right angles to the antero-posterior axis, and parallel to the segment margins (Plate 1 *a*). In the fifth stage and earlier larval stages the folds run in all directions, a pattern which results from an intrinsic expansion of the epicuticle against general constraint (Locke, 1959). In adults an equivalent expansion probably occurs, but here some polarized component of the epicuticle restricts the folding into one axis. In a series of simple and elegant experiments Locke showed that there is a gradient in each segment of *Rhodnius* which controls the orientation of the adult ripples, and that each segment is equivalent in terms of this gradient. Locke operated on the integument of fifth-stage larvae and found that:

(i) transplantation of square pieces of integument either from side to side at the same level, or from segment to segment at the equivalent level had no effect on the adult pattern;

(ii) exchange of parts taken from anterior and posterior regions of the segment, *without change in their orientation* altered the adult pattern;

(iii) squares rotated through 90 degrees in anticlockwise or clockwise direction produced S-shaped curves which were mirror images of each other.

These and other experiments indicated that the cells forming the ripples differed quantitatively down the axis of the segment (a gradient), and that when cells of different gradient values were placed together they interacted in relation to the amount and the sign of this difference. These interactions found expression in the altered orientation of ripples.

THE NATURE OF THE SEGMENTAL GRADIENT

We realized that the ripple pattern of *Rhodnius* as well as the patterns produced earlier by Piepho, could result from a segmental gradient consisting of a diffusible substance (Stumpf, 1965*a*, *b*; Lawrence, 1966). In this interpretation, the patterns produced by operations on *Rhodnius* indicate the three-dimensional landscape of concentration after diffusion. When cells from a high point in the gradient are placed adjacent to those from a low point, the gradient substance diffuses from the high cells to the low ones, resulting in a change in the level of them both and also, often, in a change in direction of the gradient slope. It was suggested that the ripples were laid down parallel to the contours of the landscape formed as a result of this diffusion. (The ripples are not themselves contours as, unlike contours, they often branch and are more or less evenly spaced.) In this model the gradient and polarity are mutually dependent; the direction of slope of the former specifying the latter.

We have recently been re-examining this model more quantitatively (Lawrence, Crick & Munro, in preparation). We have asked two main questions; first, would a diffusion gradient give rise to the patterns observed? Second, how rapidly does the diffusion occur and is it related to events in the epidermal cells?

Rhodnius is a very convenient experimental animal; the moult cycle is initiated by one large meal, and in the fifth-stage larva kept at 29 °C, ecdysis to adult follows in about 19 days. It is simple to cut out squares of integument with a piece of broken razor blade, and to transplant them or reimplant them in a different orientation. When operations are performed on unfed insects, they must be allowed to heal for at least 7 days before feeding a large meal. Operations were also performed after feeding, and these did not delay the time of ecdysis significantly.

A series of adult patterns were produced by rotating square pieces of larval integument one week before feeding (Plate 1 *b*), and these were compared with the results of computer simulations of different types of diffusion gradient.

The simplest diffusion gradient is set up between a source and a sink which each maintain different concentrations of a diffusible morphogen (Stumpf, 1967*a*; Crick, 1970). Under these conditions the effect of rotating a square piece 90 degrees and allowing diffusion for different periods of time, can be computed. The epicuticle, which expresses the cell polarity in terms of the oriented ripples, is laid down over a short period and represents a snapshot of the gradient landscape at that time. Thus the pattern could reasonably be compared with contour maps obtained from the computer after the appropriate period of diffusion. One such comparison is illustrated in Plate 1 *b*, *c*. This model would predict that diffusion would be continuous with time, so that the effects of the operation would become progressively less apparent, the pattern more 'relaxed', the longer the interval from operation to epicuticle deposition. Fifth-stage larvae of

Rhodnius were made to moult at different times after the operation by varying the feeding regimen. In particular some individuals were kept for several months, by feeding only small meals, and these individuals when they eventually moulted to adults, had very similar patterns to those insects which had moulted directly following the first meal. Attempts to correlate a measure of relaxation (the angle made between the ripples in the centre of the graft and the antero-posterior axis) with the time elapsing between the operation and cuticle deposition have been unsuccessful.

Normally only one ripple pattern can be obtained from an individual, but feeding followed by injection of 5 μg of ecdysone can induce the adult to moult again and the epidermal cells to deposit a supernumerary adult cuticle and ripple pattern. In my experiments about three weeks intervened between the deposition of the first and the second adult cuticle. In all eight cases of adults made to moult again after a 90 degrees rotation operation performed in the fifth larval stage, there was essentially no difference between the first and the second ripple pattern (Plate 2*c*, *d*). Apart from some local readjustments, the degree of relaxation was indistinguishable. These observations show that relaxation does not continue with time, and suggest that the observed patterns may represent an equilibrium position. The persistence of some effect of rotation for as long as several months, itself points to some limitation of the process of diffusion by the cells of the segment surface.

There are several possible explanations, for example:

(1) Diffusion might only be associated with particular events in the moult cycle, events which do not occur in an adult–adult moult.

(2) The cells might actively transport the morphogen against the diffusion gradient so that an equilibrium is reached (Lawrence, 1966).

(3) After an operation the cells might limit the extent of diffusion by attempting to maintain their internal concentration of the substance at their original level (Crick, 1970). In this model (model 3) the cells can be either sources or sinks depending on their new environment; and the concentration of the substance inside the cell could depend, for example, on a balance between two enzymes, one synthetic, and one degradative (as with cyclic AMP – Robison, Butcher & Sutherland, 1968). If the cells are very efficient at maintaining their original level the pattern will relax but little after operation and as the efficiency of their internal control falls, the equilibrium position becomes more and more relaxed. This model is easily computed as there is only one variable: which is a measure of the diffusion rate as compared to the efficiency with which the cells maintain their former internal concentration of the morphogen. Two equilibrium patterns produced with different values of this variable are illustrated in Plate 1*d*, *f*. Broadly the patterns are similar to those produced by diffusion alone, although the edge of the patterns, as compared to the middle, shows less relaxation.

A quantitative study of the real patterns, and the computed ones allows some discrimination between models. A comparison was made between the angle of inclination of ripples in the centre and the periphery of the pattern after a 90 degree rotation (Lawrence, Crick & Munro, in preparation). We found that the observed patterns are quite different from those produced by diffusion alone, and very similar to those predicted by model 3. These measurements probably rule out the pure diffusion hypothesis and although model 3 is consistent with them other models are not excluded.

Operations performed after feeding in *Rhodnius*, allow much less time for both wound healing and relaxation. In spite of complications at the edge of the graft which result from wound healing the degree of relaxation can be deduced from the angle of the ripples in the middle of the graft. Plates 2*a* and *b* show two typical results of such an operation, in which the ripples in the centre of the graft have only relaxed to about 5 degrees compared with the mean angle of about 30 degrees for operations performed before feeding. Because of the experiments reported above it seems unlikely that time alone is responsible for the difference between the two classes of experiments and there may therefore be other essential events.

We do not yet know what these events may be, but one idea is very appealing. It is apparent that the gradient must grow with the insect and maintain its form. If for the purposes of the following argument we adopt the model 3 described above, in which the cells attempt to maintain their internal concentration of the diffusible morphogen at a pre-set level, our results might be explained if every time a cell in the segment surface divided the daughter cell's level was not inherited from the mother cell but reset at the level in which it found itself. The cells in the margins would not be reset in this way. Normally this would allow the gradient to grow with the animal; and when equilibrium had been reached after an operation further relaxation would only occur as a result of subsequent cell divisions. Because of variable and differential cell death in *Rhodnius* (Wigglesworth, 1942) estimates of the amount of cell division are difficult, but it is of interest that in the adult–adult moult where no relaxation occurred no mitoses were observed in stained preparations and that cell density counts suggested no change in cell number. I have confirmed Locke's observation that when operations are performed in the fourth larval stage, relaxation continues during the fifth-adult moult (Plate 1*e*) (Locke, 1959) when some cell division does occur (Wigglesworth, 1940*a*, *b*).

In conclusion we believe that *Rhodnius* ripple patterns can only be explained by a gradient of some sort, which could be a concentration gradient of a diffusible substance. The importance of the segment margins as the top and bottom of the segmental gradient is shown by implantation experiments (Piepho, 1955*b*) yet as the pattern does not change with time alone and as the patterns are themselves different from those produced by diffusion alone, the gradient cannot be maintained purely by diffusion from one segment margin to the other. Some other cellular activity which limits diffusion is also required.

QUALITATIVE PATTERNS IN THE INSECT SEGMENT

A gradient embodies two types of information; it is polarized with respect to the direction of slope, and it varies quantitatively down its length. If, as we have suggested, the segment margins maintain the concentration at particular levels, then while the steepness of the gradient will vary with the size of the segment, the total concentration difference will not, and the concentration at any point will specify the position in the segment axis.

It is possible that the cells in the segment use this 'positional information' (Wolpert, 1969). To test this hypothesis it is necessary to perform transplantations prior to determination and to choose an insect which has several different structures in the integument. These experiments were undertaken on *Galleria* by Marcus (1962, 1963) even though he was unaware of Locke's work on the segmental gradient. Because of the importance of these little known experiments, and because my interpretation is somewhat different from Marcus's (see Lawrence, 1966, 1970*a*, *b*) two key examples are described below.

The adult abdominal segment of *Galleria* is divided into strips of integument of seven different kinds. On the main area of the segment surface three kinds of scales are formed, distinguished by their shape, size and ploidy of the scale-forming cells (regions 3, 2 and 1). Just anterior to the scales there is a thin ridge of tanned cuticle (region 4). The intersegmental membrane consists of three types of cuticle distinguishable by their sculpturing (regions 5, 6 and 0).

Marcus implanted pieces of larval epidermis into the body cavity of larval hosts and when retrieved after metamorphosis, he found they had made cuticle according to their prospective fate. Thus the cells of the larval segment seemed already to be determined. His next experiments were designed to test whether cells always developed in accordance with their prospective fate even when surrounded by cells of different type. Making use of a difference between the amount of heterochromatin in male and female nuclei, Marcus transplanted between male and female caterpillars, so that the grafted cells could be distinguished in the adult. He transplanted a piece of intersegmental membrane (including, in my interpretation, the posterior margin of the segment; region 0) into the middle of the segment of full-grown larvae (presumptive scales; region 2). In the adult he found that the grafted cells had made cuticle appropriate to their origin (0 cuticle), however the host cells had been influenced by the transplantation and while some formed 0 cuticle also, in addition there was a ring of type 1 scales around the graft (Fig. 1). The orientation of these scales showed that there had been corresponding alterations in the polarity of the host cells, all the scales nearby instead of pointing posteriorally, pointed towards the graft. This orientation indicated a local dip in the gradient, which had also altered the developmental fate of the cells within it. It seemed that it was the position in the gradient, rather than either the developmental history or the position in the segment, which directly determined the development of these cells. This idea that the level in the gradient, the concentration of

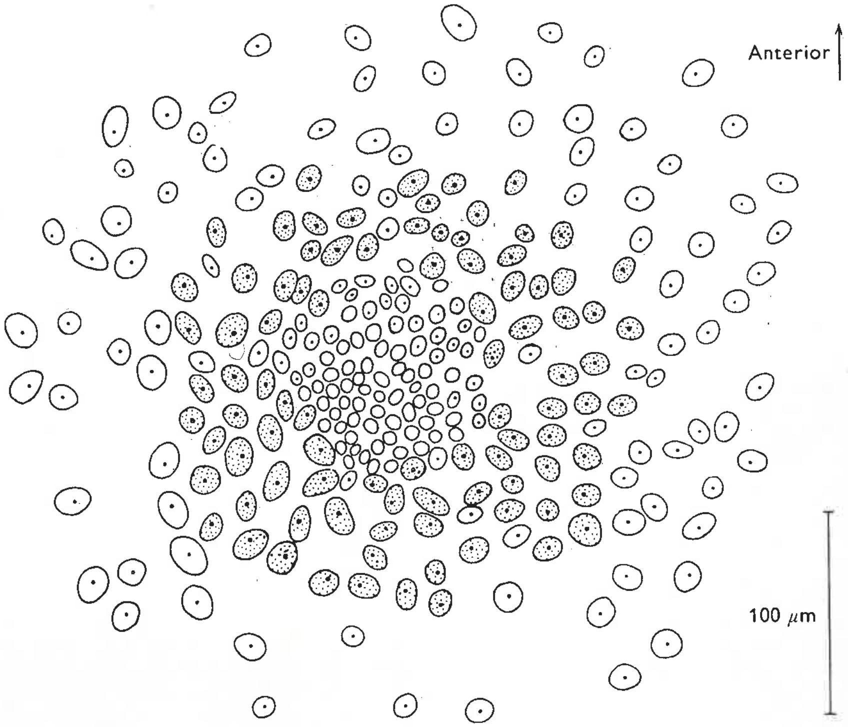

Fig. 1. Detail of Marcus's experiment I. The male grafted nuclei are undotted, the female host nuclei are dotted. The stippled nuclei from the host are the induced scale cells of type 1. (From Marcus, *Wilh. Roux. Arch. f. EntwMech.* **154**, 78, fig. 12. Berlin–Göttingen–Heidelberg: Springer 1962.)

the postulated diffusible substance, carried the positional information to the cells, was supported by Marcus's second experiment. He transplanted a larger graft which included anterior and posterior margins of adjacent segments (region 0 and 6). In this case the cells of the host, which would have developed type 2 scales if uninfluenced, made type 1 scales, and region 0 cuticle near region 0 of the graft, and, in order, cuticle of types 6, 5, 4 and 3 near region 6 (Fig. 2).

Both these experiments illustrate the dominance of the grafted pieces of margin. Just as noted by Piepho (1955*b*) the transplanted margin is capable of changing the polarity of cells at a distance. If the host (say 5) and graft (say 3) interacted evenly one would expect both host and graft cells to contribute to forming the intermediate cells (say 4). Similarly a small graft might be expected to lose its different gradient position as a result of diffusion, and develop therefore according to its new position. Yet Marcus's grafts of segment margin not only maintained their determined state, but incorporated neighbouring cells into the same tissue.

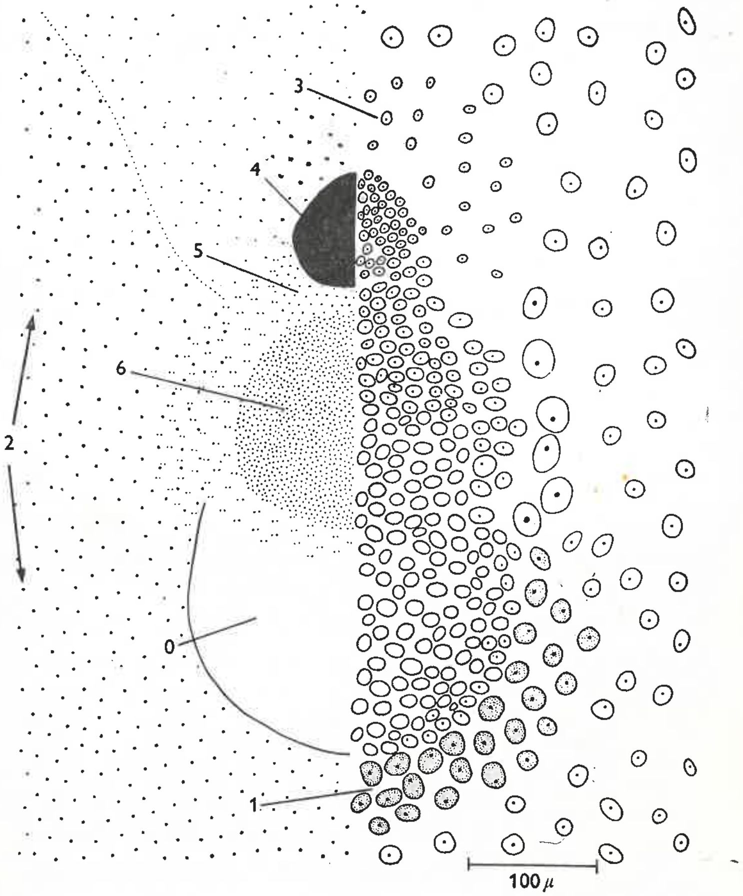

Fig. 2. Detail of Marcus's experiment II. The situation in the adult *Galleria* after transplantation of a graft including both segment margins (0 and 6) into the segment surface (region 2). Note that the succession of cuticle types is in the same order as are found in the segment. Graft nuclei are undotted, host dotted. (From Marcus, *Wilh. Roux. Arch. f. EntwMech.* **154,** 82, fig. 15. Berlin–Göttingen–Hiedelberg: Springer 1962.)

Stumpf (1966, 1967*b*) has rotated grafts which did not include segment margin but contained presumptive ridge, a thin line of tanned cuticle (region 4). This ridge is very narrow, runs parallel to the margins and might therefore be expected to follow a single contour line, in the gradient. Assuming a diffusible gradient substance, Stumpf predicted the form that the contour would take, following rotation of a piece of integument through 180 degrees, in which the presumptive ridge was eccentric. The predicted pattern after diffusion was a line and isolated ellipse (adding up to much more ridge than would have developed *in situ*), and the experimental result conformed strikingly with this prediction (Plate 2*e*, *f*).

These experiments illustrate how the segmental gradient can provide a more general model for pattern formation. In this view the level of the gradient *is* the positional information. It implies that the cell must be able to read the concentration, and moreover, as Crick (1970) has pointed out, the properties of diffusion, and the time available, usually limit the size of such gradients to a maximum of about 100 cells long.

DEVELOPMENT AND GROWTH OF THE SEGMENT

The results discussed above point to the organizing segment margins as separating one segment from another, and lead to the hypothesis that each segment is developmentally autonomous. Observations on malformed segments in *Drosophila* larvae and adults (Maas, 1948) have pointed to the segment margins as being organizers of the segment, and it is possible therefore that the development of these margins may be the initial step in embryonic segmentation (Locke, 1964).

I have several examples of *Oncopeltus* where the intersegmental membrane, which normally separates one segment from another is locally interrupted (Lawrence, 1970*a*). When the region without intersegmental membrane is long, the two segments now no longer separated fuse together to give a combined segment which has normal polarity and is of the same length as one ordinary segment. This observation also suggests that the segment margins intervene between two independently growing tissues, a hypothesis which I tested in the following way. In *Oncopeltus* we now have a number of mutations affecting pteridene synthesis (Lawrence, 1970*c*)

X-irradiation of the eggs of bugs heterozygous for these mutations leads to chromosome damage and occasionally differently coloured clones of cells of homozygous phenotype develop. The size and shape of these clones indicate the approximate number of cells at the time of irradiation and the prospective fate of the marked cell (Bryant & Schneiderman, 1970). Briefly these experiments show that at the time of abdominal segment determination there are only about ten cells in each half sternite, and that after this time all the segments grow independently. Clones formed by X-irradiation after about 12 h development at 29 °C rarely include more than one segment and cease abruptly at the intersegmental margin (Fig. 3). The insect is apparently constructed in two halves (as is also indicated by complete gynandromorphs) for the clones never cross the midline. These clones indicate that the segments grow as units, and that mitoses result in growth inwards from the two margins.

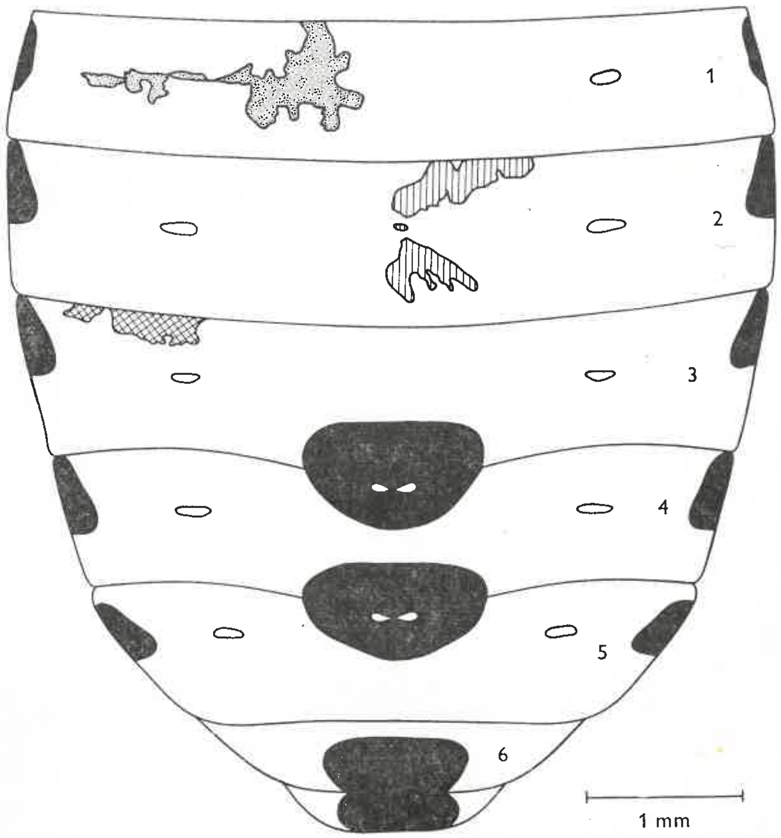

Fig. 3. Composite diagram of tergite of fifth-stage larva of *Oncopeltus* to show three typical clones produced by X-irradiation of 12–15 h eggs. Note clones stop at segment margin and do not cross midline. Clones commonly become split into two or more groups of cells.

CONCLUSION

Formally a combination of determination and a gradient mechanism which is used repeatedly can give rise to unlimited diversity of cell types. It is now established that cells can maintain their identity, their state of determination, throughout many cell divisions without expressing it by differentiation (Holtzer, Abbott, Lash & Holtzer, 1960; Hadorn, 1966). If it is allowed that the position in an axial gradient can lead to determination of this sort, let us say into ten different regions; then following growth each of these regions can be further subdivided into ten, leading to more precise determination. Indeed work on the imaginal discs of *Drosophila* has shown that determination does become progressively more precise during development (Schubiger, 1968). Moreover there is evidence that the pattern-forming process ('prepatterns' see Stern, 1968; Lawrence, 1970*a*) is equivalent in different organs, thus local patches of leg cells in the antenna (Roberts, 1964) can read their position in the antenna, but react as if they were in the *homologous* site in the leg.

The receipt of this positional information need not only lead to determination, it may also result in differential growth, or cell death or even migration, resulting of course in a change of form. Gradients may be established in two or three axes, as has been suggested by work on limb regeneration in the insect (Bodenstein, 1937, Bohn, 1965; Lawrence, 1970*a*). It is even conceivable that these gradients could be identical, if they were established at different times. It is of interest that in one case where the timing of axial organization is known (the retina of amphibians, Székely, 1954; Jacobson, 1968) the two axes are determined at different times.

The onus on those who work on gradients is to find the substances involved. Unfortunately, the experiments on *Rhodnius* point to a highly homeostatic system, which is therefore unlikely to yield a helpful assay. We need to detect a transient change in the polarity of cells, and need to apply test substances just before that polarity is expressed, otherwise on all the gradient models we have suggested, no trace will remain of it.

I am grateful to many colleagues for valuable discussions and particularly to Dr Francis Crick for his advice and encouragement.

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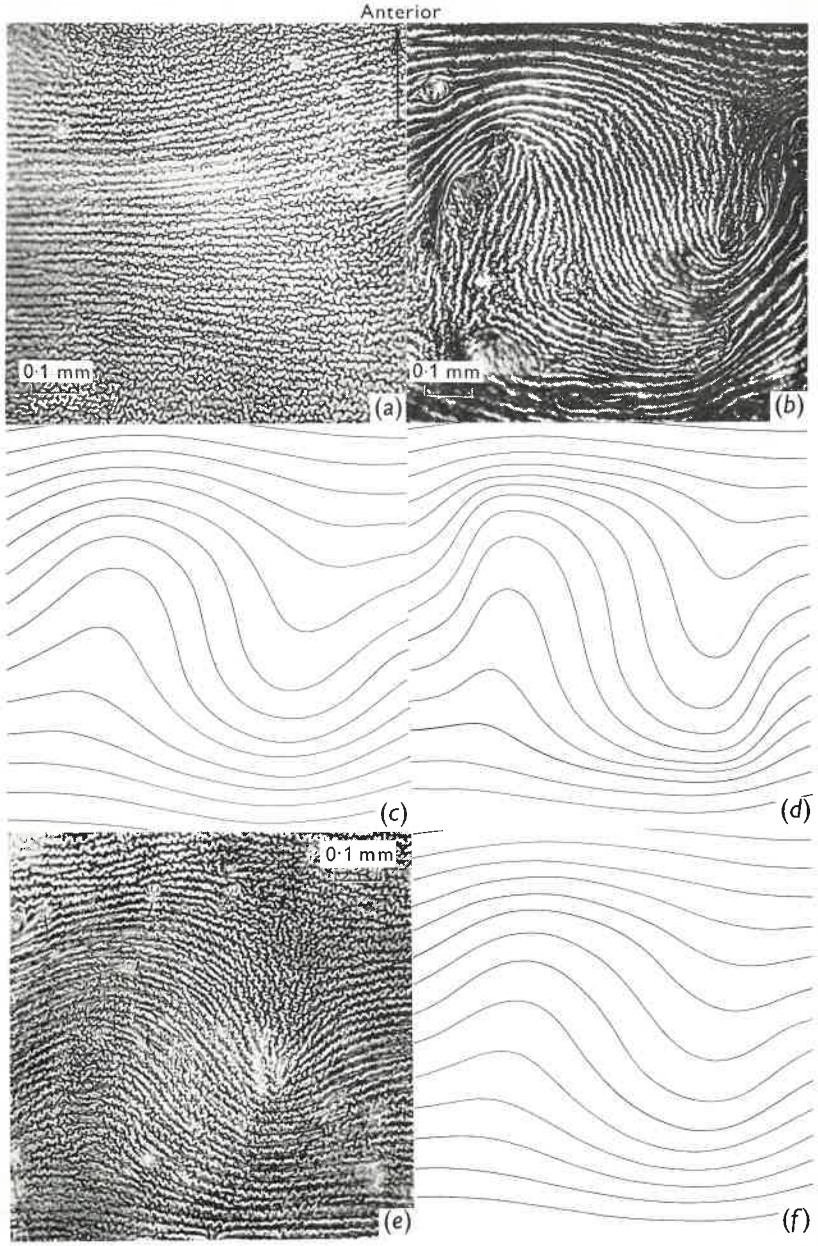
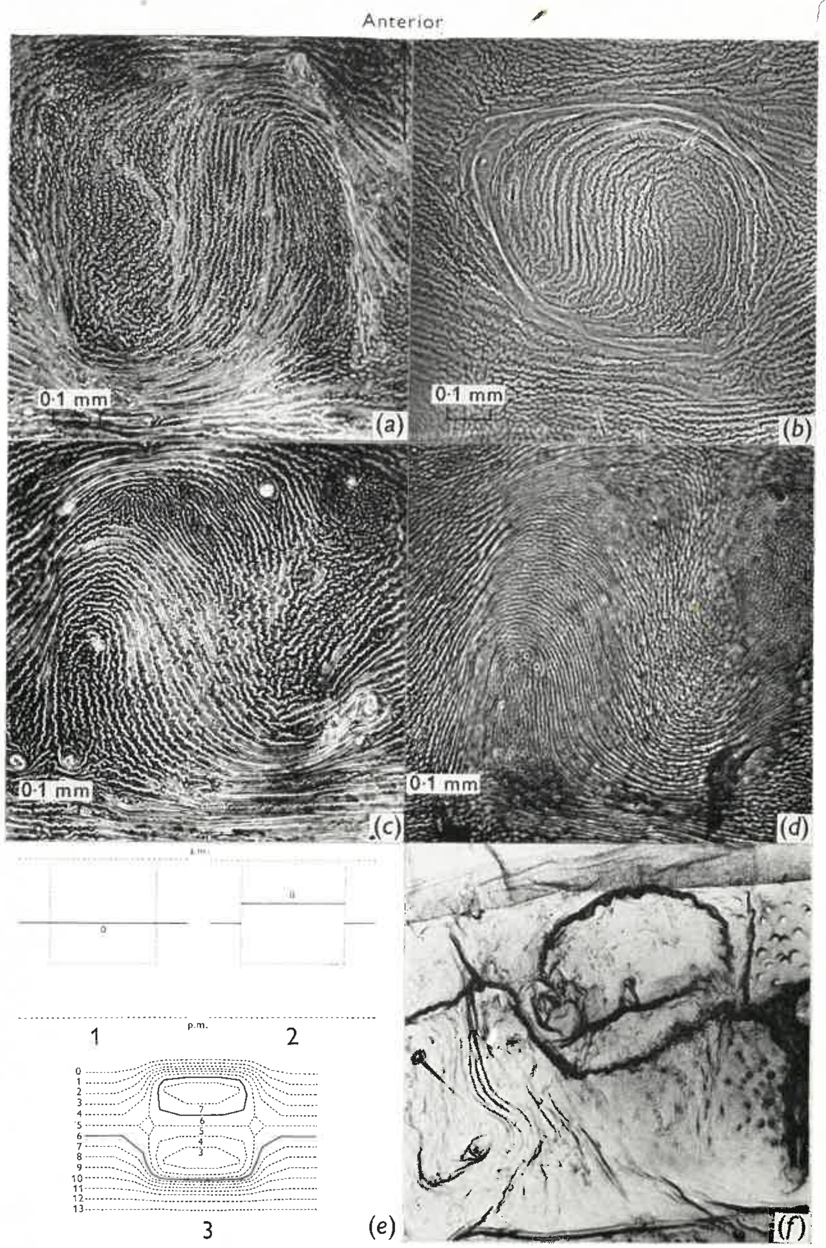
PLATE I



(*a*) Cuticle from adult abdominal tergite of *Rhodnius*, to show oriented ripples. Phase contrast, scale = 0·1 mm.

(*b*)–(*f*). Adult ripple patterns after 90 degree rotation of square pieces of integument in larvae. (*b*) shows pattern after operation in fifth-stage larva before feeding. (*e*) shows pattern after operation in fourth-stage larva before feeding. (*d*) and (*f*) are equilibrium patterns for gradient model 3 (see page 382) and (*c*) for comparison with (*d*), assumes a diffusion gradient set up between a source and a sink and represents a contour map after diffusion for a certain period of time following 90 degree rotation.

PLATE 2



(*a*) and (*b*). Two typical adult ripple patterns produced by 90 degree rotation operation performed on fifth-stage larvae 5 days after feeding. Note that the host-graft junction is still affected by wounding and that the central ripples of the graft are approximately parallel to the antero-posterior axis.

(*c*) and (*d*). Two ripple patterns produced by the same individual. The orientation of ripples in the first adult pattern (*c*) and the second (*d*) are very similar, although the nature of the cuticle itself is different. Phase contrast, scale = 0·1 mm.

(*e*) and (*f*). A square of larval cuticle of *Galleria* in which the presumptive ridge (contour 6) is slightly eccentric (1), is rotated through 180 degrees (2). After some diffusion the predicted pattern is as shown in (*e*) (3). The experimental result is in (*f*). (From Stumpf, 1967*b*.)

POSITIONAL INFORMATION AND PATTERN REGULATION IN REGENERATION OF HYDRA

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The concept of positional information (Wolpert, 1969, 1970) was introduced in order to provide a conceptual framework within which one could analyse pattern formation and regulation. The basic ideas associated with it are that pattern formation is essentially a two-step process; first the assignment of positional information to the cells in a co-ordinate system, and subsequently the interpretation of this positional information by the cells leading to molecular differentiation. The interpretation of positional information depends mainly on the cell's genome and developmental history. It was further postulated, partly in opposition to 'special substance' views of development, that the mechanism for establishing positional information might be universal. The concept of positional information was originally developed for regulative systems which are characterized by having intercellular communication such that removal of a region results in the remainder regulating so that the lost part is not missing from the final pattern. It may, nevertheless, be possible to extend the concept to mosaic systems (Wolpert, 1971).

Positional information could be regarded as being an extension of gradient theories of the type put forward by Child (1941) but differs in its emphasis on the specification of boundary values and quantitative variation providing effectively a co-ordinate system. A major feature is its attempt to put gradient theory onto a quantitative basis and to draw attention to the various ways in which a gradient which might provide positional information could be established. It also defines polarity in terms of the gradient. Regeneration, regarded in these terms, is the re-assignment of positional information when a system is perturbed: that is the re-establishment of boundary values and the form of the gradient. The two main ways in which this might occur in a simple uni-axial system – the French Flag – are illustrated in Fig. 1, and correspond to classic concepts of epimorphosis and morphallaxis. Consider a line of cells each capable of forming blue, white or red pigments, and in the form of the French Flag (Wolpert, 1968). If, for example, the blue and part of the white were